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(71) Applicant *(for all designated States except US)*: **PLIVA D.D.** [HR/HR]; Ulica grada Vukovara 49, 10000 Zagreb (HR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LOPOTAR, Nevenka** [HR/HR]; Šublinov brijeg 116, 10090 Zagreb (HR). **NARANDJA, Amalija** [HR/HR]; Bartula Kašića 6, 10000 Zagreb (HR). **MUTAK, Stjepan** [HR/HR]; Jagnedje 1, 10090 Zagreb (HR).

(74) Common Representative: **PLIVA D.D.**; Vasiljevic, Vesna, Ulica grada Vukovara 49, 10000 Zagreb (HR).

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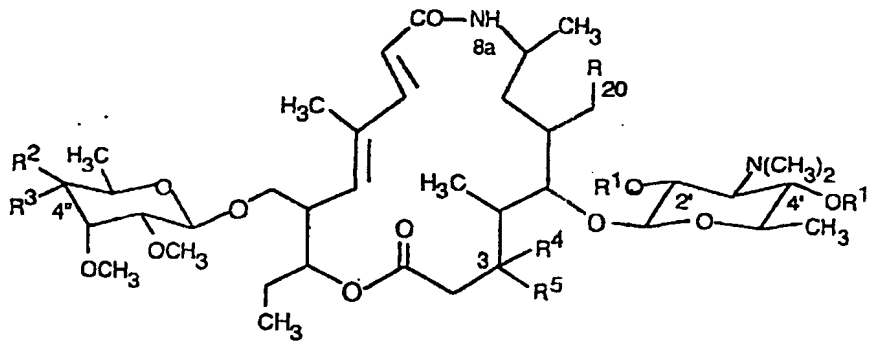
(54) Title: DERIVATIVES OF 4'-DEMYCAROSYL-8a-AZA-8a-HOMOTYLOSIN



(I)

(57) Abstract: The invention relates to derivatives of 4'-demycarosyl-8a-aza-8a-homotylosin of formula (I) wherein R represents CHO, $CH(OCH_3)_2$) or $CH_2N[CH_2(C_6H_5)]_2$, R^1 represents H or C_1-C_3 acyl, R^2 represents OR^6 and R^6 represents H or C_1-C_3 acyl, R^3 represents H or R^2 and R^3 together represent =O, R^4 represents OH, R^5 represents H or R^4 and R^5 together represent =O, and to a process for the preparation thereof. Novel derivatives show antibacterial action and may also be used as intermediates for preparing novel 17-membered azalide antibiotics.

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DERIVATIVES OF 4'-DEMYCAROSYL-8a-AZA-8a-HOMOTYLOSIN

Technical Field

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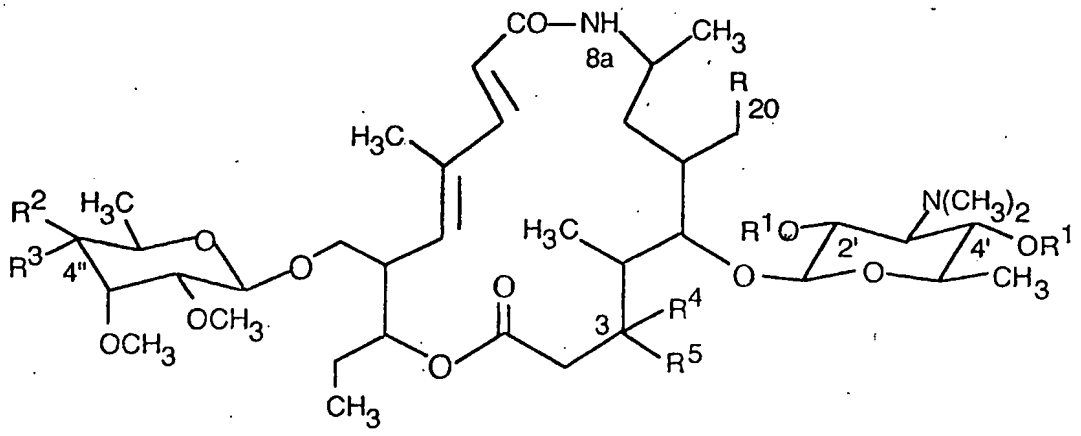
Technical Problem

The present invention relates to novel compounds from the class of 17-membered azalides having an antibacterial action. More particularly, the invention relates to derivatives of 4'-demycarosyl-8a-aza-8a-homotylosin of the formula I



I

wherein R represents CHO, $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$,
R^1 represents H or C_1-C_3 acyl,
R^2 represents OR^6 and R^6 represents H or C_1-C_3 acyl,
R^3 represents H or R^2 and R^3 together represent =O,
R^4 represents OH,
R^5 represents H or R^4 and R^5 together represent =O,
and to a process for the preparation thereof.

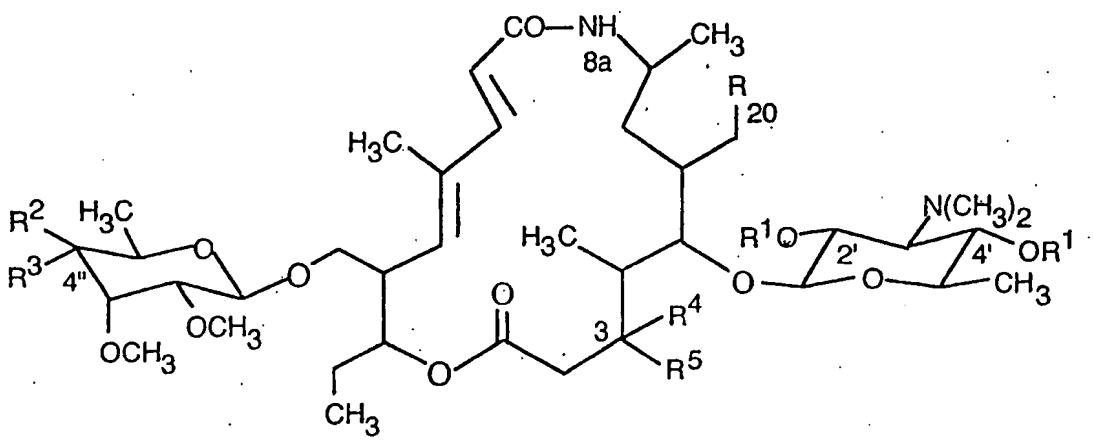
Prior Art

4'-Demycarosyl-8a-aza-8a-homotylosin, a novel semisynthetic macrolide from the class of 17-membered azalides, was prepared by a double transformation of C-9 ketone of the 16-membered antibiotic 4'-demycarosyl-tylosin (R. L. Hamill, Antibiotics and Chemotherapy 11, 328 (1961); A. Narandja et al, EP 0 287 082 B1; N. Lopotar et al, EP 0 410 433 B1). By reductive amination of C-20 aldehyde group in the presence of formic acid (Wallach reaction, J. March: "Advanced Organic Chemistry", third ed. 6-15 p. 799 Wiley, New York, 1985) there was prepared 4'-demycarosyl-20-deoxo-20-dibenzylamino-8a-aza-8a-homotylosin (N. Lopotar, HR Patent Application P940962A, 30.11.1994).

C_1-C_3 acyl esters of 4'-demycarosyl-8a-aza-8a-homotylosin and of 4'-demycarosyl-20-deoxo-20-dibenzylamino-8a-aza-8a-homotylosin as well as 4"-deoxy-4"-oxo- and 3-deoxy-3-oxo derivatives of 4'-demycarosyl-8a-aza-8a-homotylosin and of 4'-demycarosyl-20-deoxo-20-dibenzylamino-8a-aza-8a-homotylosin, C_1-C_3 acyl esters thereof and a process for the preparation thereof have hitherto not been disclosed in Prior Art.

Detailed Description of the Invention

According to the present invention derivatives of 4'-demycarosyl-8a-aza-8a-homotylosin of the formula I



I

wherein R represents CHO, $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$,

R^1 represents H or C_1-C_3 acyl,

R^2 represents OR^6 and R^6 represents H or C_1-C_3 acyl,

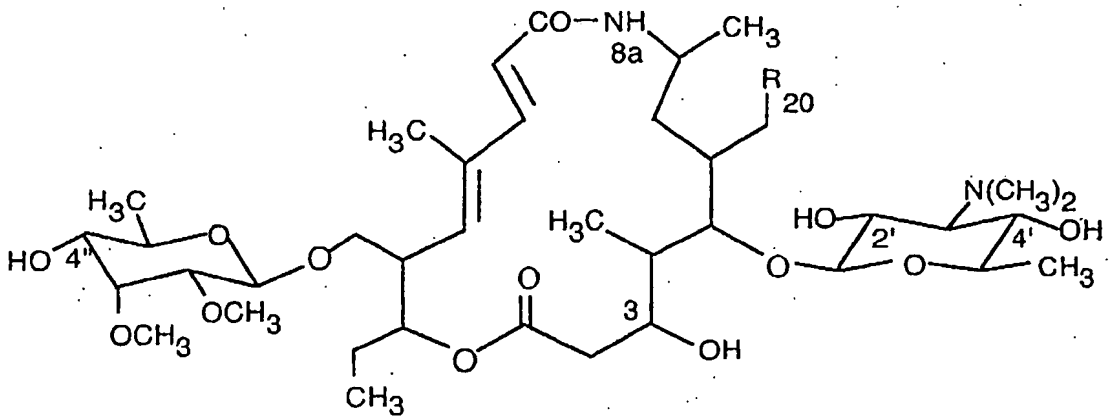
R^3 represents H or R^2 and R^3 together represent =O,

R^4 represents OH,

R^5 represents H or R^4 and R^5 together represent =O,

may be prepared in such a way that

4'-demycarosyl-8a-aza-8a-homotylosin 20-dimethylacetal of the formula IIa and 4'-demycarosyl-20-deoxo-20-dibenzylamino-8a-aza-8a-homotylosin of the formula IIb



IIa R = $CH(OCH_3)_2$

IIb R = $CH_2N[CH_2(C_6H_5)]_2$

are subjected to

A) an O-acylation with anhydrides of C_1-C_3 carboxylic acids, preferably with acetic acid anhydride in methylene chloride during 15 minutes to 1 hour at room temperature, and the obtained compounds of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1 represents $COCH_3$, R^2 represents OR^6, wherein R^6 represents H, R^3 and R^5 are the same and represent H and R^4 represents OH,

are optionally subjected to

A1) an O-acylation with anhydrides of C_1-C_3 carboxylic acids, preferably with acetic acid anhydride in methylene chloride in the presence of an organic base, preferably triethyl amine and 4-dimethylaminopyridine as a catalyst during 30 hours at room temperature, and the obtained compounds of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1 represents $COCH_3$, R^2 represents OR^6, wherein R^6 represents $COCH_3$, R^3 and R^5 are the same and represent H and R^4 represents OH,

are optionally subjected to

B) an oxidation reaction with N(3-dimethylamino-propyl)-N'ethyl carbodiimide hydrochloride in the presence of dimethylsulfoxide and pyridine trifluoroacetate as a catalyst in an inert solvent, preferably methylene chloride, during 2 to 6 hours at a temperature from 10°C to room temperature, and the obtained compounds of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1 represents $COCH_3$, R^2 represents OR^6, wherein R^6 represents $COCH_3$, R^3 represents H and R^4 and R^5 together represent =O,

are optionally subjected to

C) methanolysis at room temperature for 2 days and the obtained compounds of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1 and R^3 are the same and represent H, R^2 represents OR^6, wherein R^6 represents $COCH_3$, and R^4 and R^5 together represent =O,

are optionally subjected to

C1) an alkaline methanolysis in a mixture of methanol and 25% ammonia (4:1) at a temperature from 5°C to room temperature during 20 to 60 hours to obtain compounds of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1 and R^3 are the same and represent H, R^2 represents OR^6, wherein R^6 represents H, and R^4 and R^5 together represent =O;

or the compound obtained according to process C1

of the formula I, wherein R represents $CH(OCH_3)_2$, R^1 and R^3 are the same and represent H, R^2 represents OR^6, wherein R^6 represents H, and R^4 and R^5 together represent =O,

is optionally subjected to

D) a hydrolysis of the acetal in a mixture of acetonitrile and 0.1 N hydrochloric acid (1:1) for 2 hours at room temperature to obtain the compound of the formula I, wherein R represents a CHO group, R^1 and R^3 are the same and represent H, R^2 represents OR^6, wherein R^6 represents H, and R^4 and R^5 together represent =O;

or compounds obtained according to process A

of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1 represents $COCH_3$, R^2 represents OR^6, wherein R^6 represents H, R^3 and R^5 are the same and represent H and R^4 represents OH,

are optionally subjected to oxidation in the manner disclosed in B,

and the obtained compounds of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1 represents $COCH_3$, R^2 and R^3 together represent =O, R^4 represents OH and R^5 represents H,

are optionally subjected to methanolysis in the manner disclosed in C,

to obtain compounds of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1 and R^5 are the same and represent H, R^2 and R^3 together represent =O and R^4 represents OH;

or the compound obtained according to process B
of the formula I, wherein R represents a $CH(OCH_3)_2$ group, R^1 represents $COCH_3$, R^2 and R^3 together represent =O, R^4 represents OH and R^5 represents H,

is optionally subjected to a hydrolysis of acetal in the manner disclosed in D,
and the obtained compound of the formula I, wherein R represents a CHO group, R^1 represents $COCH_3$, R^2 and R^3 together represent =O, R^4 represents OH and R^5 represents H,

is optionally subjected to methanolysis in the manner disclosed in C,
to obtain the compound of the formula I, wherein R represents a CHO group, R^1 and R^5 are the same and represent H, R^2 and R^3 together represent =O and R^4 represents OH;

or the compound obtained according to process A
of the formula I, wherein R represents $CH(OCH_3)_2$, R^1 represents $COCH_3$, R^2 represents OR^6, wherein R^6 represents H, R^3 and R^5 are the same and represent H and R^4 represents OH,

is optionally subjected to a hydrolysis of acetal in the manner disclosed in D,
to obtain a compound of the formula I wherein R represents CHO, R^1 represents $COCH_3$, R^2 represents OR^6, wherein R^6 represents H, R^3 and R^5 are the same and represent H and R^4 represents OH;

or compounds obtained according to process A1
of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1 represents $COCH_3$, R^2 represents OR^6, wherein R^6 represents $COCH_3$, R^3 and R^5 are the same and represent H and R^4 represents OH,

are optionally subjected to methanolysis in the manner disclosed in C,
to obtain compounds of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1, R^3 and R^5 are the same and represent H, R^2 represents OR^6, wherein R^6 represents $COCH_3$, and R^4 represents OH;

or the compound obtained according to process A1
of the formula I, wherein R represents $CH(OCH_3)_2$, R^1 represents $COCH_3$, R^2 represents OR^6, wherein R^6 represents $COCH_3$, R^3 and R^5 are the same and represent H and R^4 represents OH,

is optionally subjected to a hydrolysis of acetal in the manner disclosed in D,
and the obtained compound of the formula I, wherein R represents CHO, R^1 represents $COCH_3$, R^2 represents OR^6, wherein R^6 represents $COCH_3$, R^3 and R^5 are the same and represent H and R^4 represents OH,

is optionally subjected to methanolysis in the manner disclosed in C,
to obtain the compound of the formula I, wherein R represents CHO, R^1, R^3 and R^5 are the same and represent H, R^2 represents OR^6, wherein R^6 represents $COCH_3$, and R^4 represents OH.

According to the present invention novel compouds are isolated by conventional processes of extraction from aqueous solutions of halogenated hydrocarbons such as methylene chloride or chloroform and by evaporating the organic solvent to a dry residue. Optionally, the separation of the reaction products or the purification of the products for spectral analyses is carried out by flash chromatography on a silica gel column (Merck & Co., Silicagel 60, 230-400 mesh/ASTM) in a solvent sistem: CH_2Cl_2-CH_3OH-conc. NH_4OH (90:9:1.5, system A), CH_2Cl_2-CH_3OH (90:9, system B) or $CHCl_3$-CH_3COCH_3 (7:3, system C).

The structure of the novel compounds was confirmed by spectrometric methods and mass analysis.

The novel compounds show antibacterial action and may be also used as intermediates for preparing novel 17-membered azalide antibiotics.

The invention is illustrated and in no way limited by the following Examples.

Example 1

4'-Demycarosyl-2',4'-di-O-acetyl-8a-aza-8a-homotylosin 20-dimethylacetal (1)

4'-Demycarosyl-8a-aza-8a-homotylosin 20-dimethylacetal (5.0 g, 6.02 mmol) was dissolved in dry methylene chloride (50 ml), acetic anhydride (2.0 ml) was added and it was stirred for 15 minutes at room temperature. The reaction mixture was poured into a water/ice mixture (500 ml) and extracted twice with methylene chloride at pH 8.5. The combined organic extracts were washed with a saturated $NaHCO_3$ solution and water, dried (K_2CO_3) and evaporated at reduced pressure to give a TLC homogeneous product (1) (5.38 g; 97.8 %).

TLC: Rf (B) 0.44; Rf (C) 0.22.

IR (KBr) cm^{-1} 1749, 1657, 1620, 1544, 1455, 1375, 1229, 1170, 1063.

^1H NMR ($CDCl_3$) δ ppm 7.16 (H-11), 5.69 (H-10), 5.66 (H-13), 4.96 (8a-NH) exchangeable with D_2O, 4.88 (H-2'), 4.76 (H-4'), 4.63 (H-20), 4.58 (H-1"), 4.33 (H-1'), 4.17 (H-8), 3.61 (3"-OCH_3), 3.47 (2"-OCH_3), 3.56 (2x20-OCH_3), 2.33 /3'-$N(CH_3)_2$/, 2.05 ($COCH_3$), 2.03 ($COCH_3$), 1.74 (H-22), 1.17 (H-21).

^{13}C NMR ($CDCl_3$) δ ppm 179.1 (C-1), 169.8, 169.4 (2x$COCH_3$), 166.2 (9-CONH), 144.7 (C-11), 138.2 (C-13), 134.9 (C-12), 119.2 (C-10), 103.5 (C-20), 102.0 (C-1'), 100.9 (C-1"), 72.5 (C-4"), 71.4 (C-4'), 70.3 (C-2'), 65.6 (C-3), 61.5 (3"-OCH_3), 59.4 (2"-OCH_3), 50.4 (2x20-OCH_3), 42.7 (C-8), 42.5 (C-4), 41.0 /3'-$N(CH_3)_2$/, 40.5 (C-2), 34.3 (C-19), 21.8, 20.9 (2x$COCH_3$), 21.9 (C-21), 12.6 (C-22), 8.3 (C-18).

FAB (MH^+) 917.

Example 2

4'-Demycarosyl-2',4'-di-O-acetyl-20-deoxo-20-dibenzylamino-8a-aza-8a-homotylosin (2)

4'-Demycarosyl-20-deoxo-20-dibenzylamino-8a-aza-8a-homotylosin (2.8 g, 2.90 mmol) was dissolved in dry methylene chloride (30 ml), acetic anhydride (1.3 ml, 13.76 mmol) was added and it was stirred for 15 minutes at room temperature. The reaction mixture was poured into a water/ice mixture (300 ml) and extracted twice with methylene chloride at pH 6.5. The combined organic extracts were washed with a saturated $NaHCO_3$ solution and water, dried (K_2CO_3) and evaporated at reduced pressure to give a TLC homogeneous product (**2**) (3.02 g; 98.9 %).

TLC: Rf (B) 0.38; Rf (C) 0.23.

IR (KBr) cm^{-1} 1749, 1651, 1633, 1548, 1454, 1374, 1231, 1169, 1059.

^1H NMR ($CDCl_3$) δ ppm 7.25 ~ 7.41 (phenyl), 7.10 (H-11), 5.70 (H-13), 5.65 (H-10), 4.89 (8a-NH) exchangeable with D_2O, 4.84 (H-2'), 4.74 (H-4'), 4.60 (H-1"), 4.15 (H-1'), 3.62 (3"-OCH_3), 3.61 (20-N-CH_2-phenyl), 3.58 (20-CH_2-phenyl), 3.51 (2"-OCH_3), 2.32 /3'-$N(CH_3)_2$/, 2.06 ($COCH_3$), 2.00 ($COCH_3$), 1.72 (H-22), 1.12 (H-21).

^{13}C NMR ($CDCl_3$) δ ppm 173.4 (C-1), 169.9, 169.5 (2x$COCH_3$), 166.1 (9-CONH), 144.8 (C-11), 137.9 (C-13), 135.2 (C-12), 119.3 (C-10), 102.3 (C-1'), 101.0 (C-1"), 72.5 (C-4"), 71.4 (C-4'), 70.4 (C-2'), 66.0 (C-3), 61.5 (3"-OCH_3), 59.5 (2"-OCH_3), 52.2 (C-20), 42.9 (C-8), 42.4 (C-4), 41.0 /3'-$N(CH_3)_2$/, 38.7 (C-2), 29.4 (C-19), 21.8 (C-21), 21.1, 21.0 (2x$COCH_3$), 12.7 (C-22), 8.4 (C-18), 20-$N(CH_2C_6H_5)_2$, 139.8, 129.1, 128.0, 126.6, 57.9.

FAB (MH^+) 1052.

Example 3

4'-Demycarosyl-2',4',4"-tri-O-acetyl-8a-aza-8a-homotylosin 20-dimethylacetal (3)

Compound 1 (4.0 g, 4.37 mmol) was dissolved in dry methylene chloride (100 ml), triethyl amine (7.0 ml), 4-dimethylaminopyridine (0.12 g) and acetic anhydride (0.42 ml, 4.45 mmol) were added and then the reaction solution was left to stand for 26

hours at room temperature. The isolation of the product was carried out in the manner disclosed in Example 1 to give a TLC homogeneous product (3) (4.08 g; 97.7 %).

TLC: Rf (A) 0.65; Rf (C) 0.54.

IR (KBr) cm^{-1} 1749, 1655, 1618, 1546, 1454, 1374, 1233, 1171, 1052.

^1H NMR ($CDCl_3$) δ ppm 7.16 (H-11), 5.69 (H-10), 5.65 (H-13), 4.89 (8a-NH) exchangeable with D_2O, 4.88 (H-2'), 4.76 (H-4'), 4.64 (H-1"), 4.59 (H-20), 4.33 (H-1'), 4.18 (H-8), 3.52 (3"-OCH_3), 3.46 (2"OCH_3), 3.36 (20-OCH_3), 3.35 (20-OCH_3), 2.33 /3'-$N(CH_3)_2$/, 2.12 ($COCH_3$), 2.05 ($COCH_3$), 2.03 ($COCH_3$), 1.74 (H-22), 1.16 (H-21).

^{13}C NMR ($CDCl_3$) δ ppm 173.1 (C-1), 170.1, 169.8, 169.4 (3x$COCH_3$), 166.1 (9-CONH), 144.7 (C-11), 138.0 (C-13), 134.9 (C-12), 119.2 (C-10), 103.7 (C-20), 102.1 (C-1'), 100.9 (C-1"), 74.5 (C-4"), 71.4 (C-4'), 70.3 (C-2'),. 65.6 (C-3), 61.3 (3"-OCH_3), 59.3 (2"-OCH_3), 53.7 (20-OCH_3), 50.6 (20-OCH_3), 42.7 (C-8), 42.6 (C-4), 41.0 /3'-$N(CH_3)_2$/, 40.5 (C-2), 34.5 (C-19), 21.9, (C-21), 21.1, 21.0, 20.7 (3x$COCH_3$), 12.7 (C-22), 8.3 (C-18).

FAB (MH^+) 959.

Example 4

4'-Demycarosyl-2',4',4"-tri-O-acetyl-20-deoxo-20-dibenzylamino-8a-aza-8a-homotylosin (4)

Compound 2 (2.8 g, 2.66 mmol) was dissolved in dry methylene chloride (60 ml), triethyl amine (3.7 ml), 4-dimethylaminopyridine (0.07 g) and acetic anhydride (0.25 ml, 1.64 mmol) were added and then the reaction solution was left to stand for 26 hours at room temperature. The isolation of the product was carried out in the manner disclosed in Example 1 to give a TLC homogeneous product (4) (2.7 g; 92.9 %).

TLC: Rf (B) 0.55; Rf (C) 0.47.

IR (KBr) cm^{-1} 1747, 1651, 1632, 1538, 1453, 1372, 1233, 1170, 1051.

^1H NMR ($CDCl_3$) δ ppm 7.22 ~ 7.41 (phenyl), 7.10 (H-11), 5.70 (H-13), 5.65 (H-10),

4.91 (8a-NH) exchangeable with D_2O, 4.86 (H-2'), 4.74 (H-4'), 4.66 (H-1"), 4.46 (H-4"), 4.15 (H-1'), 3.61 (2x20-N-CH_2-phenyl), 3.53 (3"-OCH_3), 3.50 (2"-OCH_3), 2.32 /3'-N(CH_3)$_2$/, 2.12 ($COCH_3$), 2.06 ($COCH_3$), 2.00 ($COCH_3$), 1.72 (H-22), 1.12 (H-21), 0.78 (H-18).

^{13}C NMR ($CDCl_3$) δ ppm 173.3 (C-1), 170.1, 169.9, 169.5 (3x$COCH_3$), 166.1 (9-CONH), 144.8 (C-11), 137.9 (C-13), 135.2 (C-12), 119.3 (C-10), 102.3 (C-1'), 101.0 (C-1"), 74.6 (C-4"), 71.4 (C-4'), 70.4 (C-2'), 66.0 (C-3), 61.5 (3"-OCH_3), 59.3 (2"-OCH_3), 52.2 (C-20), 42.9 (C-8), 42.4 (C-4), 41.0 /3'-N(CH_3)$_2$/, 38.7 (C-2), 29.4 (C-19), 21.8 (C-21), 21.1, 21.0, 20.7 (3x$COCH_3$), 12.7 (C-22), 8.4 (C-18),
20-N($CH_2C_6H_5$)$_2$, 139.8, 129.1, 128.0, 126.6, 57.9.

FAB (MH^+) 1094.

Example 5

4'-Demycarosyl-2',4'-di-O-acetyl-4"-deoxy-4"-oxo-8a-aza-8a-homotylosin 20-dimethylacetal (5)

A solution of pyridine trifluoroacetate (1.0 g, 5.24 mmol) in methylene chloride (10 ml) was added drop by drop at 15°C to a solution of the compound **1** (1.0 g, 1.09 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.0 g, 5.22 mmol) and dimethyl sulfoxide (1.0 ml, 14.10 mmol) in methylene chloride (20 ml). The reaction mixture was stirred for 3 hours at room temperature, then poured into water (150 ml) and after separating the organic layer, it was extracted two more times with methylene chloride. The combined organic extracts were washed with a saturated $NaHCO_3$ solution and water, dried (K_2CO_3) and evaporated at reduced pressure to a dry residue. The obtained crude product (0.95 g) was purified by flash chromatography on a silica gel column using the solvent system B to give a TLC homogeneous product (5) (0.45 g).

TLC: Rf (B) 0.52.

IR (KBr) cm^{-1} 1749, 1657, 1620, 1542, 1455, 1375, 1230, 1172, 1060.

^{1}H NMR ($CDCl_3$) δ ppm 7.16 (H-11), 5.71 (H-10), 5.64 (H-13), 4.97 (8a-NH) exchangeable with D_2O, 4.88 (H-2'), 4.76 (H-4'), 4.60 (H-20), 4.63 (H-1"), 4.33 (H-1'), 4.17 (H-8), 3.98 (H-5"), 3.78 (H-3"), 3.58 (3"-OCH_3), 3.52 (2"-OCH_3), 3.36 (20-OCH_3), 3.35 (20-OCH_3), 3.30 (H-2"), 2.33 /3'-$N(CH_3)_2$/, 2.05 ($COCH_3$), 2.03 ($COCH_3$), 1.76 (H-22), 1.34 (H-6"), 1.17 (H-21).

^{13}C NMR ($CDCl_3$) δ ppm 202.4 (C-4"), 173.1 (C-1), 169.9, 169.5 (2x$COCH_3$), 166.1 (9-CONH), 144.6 (C-11), 137.6 (C-13), 135.3 (C-12), 119.5 (C-10), 103.6 (C-20), 103.0 (C-1"), 102.1 (C-1'), 85.3 (C-3"), 84.2 (C-2"), 73.3 (C-5"), 71.3 (C-4'), 70.3 (C-2'), 65.6 (C-3), 60.2 (3"-OCH_3), 59.1 (2"-OCH_3), 53.7 (20-OCH_3), 50.5 (20-OCH_3), 42.7 (C-8), 42.6 (C-4), 41.0 /3'-$N(CH_3)_2$/, 40.7 (C-2) 34.4 (C-19), 21.9 (C-21), 21.1, 21.0 (2x$COCH_3$), 14.0 (C-6"), C-12.7 (C-22), 8.3 (C-18).

FAB (MH^+) 915.

Example 6

4'-Demycarosyl-2',4'-di-O-acetyl-4"-deoxy-4"-oxo-20-deoxo-20-dibenzylamino-8a-aza-8a-homotylosin (6)

A solution of pyridine trifluoroacetate (0.6 g, 3.11 mmol) in methylene chloride (6 ml) was added drop by drop at 15°C to a solution of the compound 2 (0.6 g, 0.57 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.6 g, 3.14 mmol) and dimethyl sulfoxide (0.45 ml, 6.35 mmol) in methylene chloride (20 ml). The reaction mixture was stirred for 5 hours at room temperature. The isolation of the product was carried out in the manner disclosed in Example 5. The obtained crude product (0.54 g) was purified by flash chromatography on a silica gel column using the solvent system B to give a TLC homogeneous product (6) (0.28 g).

TLC: Rf (B) 0.48; Rf (C) 0.33.

IR (KBr) cm^{-1} 1747, 1651, 1633, 1548, 1454, 1372, 1231, 1058.

^{1}H NMR ($CDCl_3$) δ ppm 7.25 ~ 7.41 (phenyl), 7.12 (H-11), 5.70 (H-13), 5.65 (H-10), 4.94 (8a-NH) exchangeable with D_2O, 4.82 (H-2'), 4.74 (H-4'), 4.65 (H-1"),

4.15 (H-1'), 3.98 (H-5"), 3.78 (H-3"), 3.62 (20-N-CH_2-phenyl), 3.58 (20-CH_2-phenyl), 3.55 (3"-OCH_3), 3.49 (2"-OCH_3), 2.32 /3'-$N(CH_3)_2$/, 2.06 ($COCH_3$), 2.00 ($COCH_3$), 1.74 (H-22), 1.36 (H-6"), 1.12 (H-21).

^{13}C NMR ($CDCl_3$) δ ppm 202.4 (C-4"), 173.4 (C-1), 169.8, 169.3 (2x$COCH_3$), 166.1 (9-CONH), 144.6 (C-11), 137.0 (C-13), 135.6 (C-12), 119.6 (C-10), 103.0 (C-1"), 102.2 (C-1'), 85.3 (C-3"), 84.8 (C-2"), 73.3 (C-5"), 71.4 (C-4'), 70.4 (C-2'), 65.9 (C-3), 60.3 (3"-OCH_3), 59.1 (2"-OCH_3), 52.2 (C-20), 42.9 (C-8), 42.4 (C-4), 40.9 /3'-$N(CH_3)_2$/, 38.7 (C-2), 29.4 (C-19), 21.8 (C-21), 21.1, 21.0 (2x$COCH_3$), 14.0 (C-6"), 12.8 (C-22), 8.4 (C-18),
20-$N(CH_2C_6H_5)_2$ 139.6, 129.9, 128.0, 126.6, 57.8.

FAB (MH^+) 1050.

Example 7

4'-Demycarosyl-2',4',4"-tri-O-acetyl-3-deoxy-3-oxo-8a-aza-8a-homotylosin 20-dimethylacetal (7)

A solution of pyridine trifluoroacetate (3.0 g, 15.72 mmol) in methylene chloride (30 ml) was added drop by drop at 15°C to a solution of the compound **3** (2.0 g, 2.09 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.0 g, 15.66 mmol) and dimethyl sulfoxide (2.9 ml, 40.89 mmol) in methylene chloride (50 ml). The reaction mixture was stirred for 3 hours at room temperature. The isolation of the product was carried out in the manner disclosed in Example 5. The obtained crude product (1.95 g) was purified by flash chromatography on a silica gel column using the solvent system C to give a TLC homogeneous product (7) (1.3 g).

TLC: Rf (C) 0.58.

IR (KBr) cm^{-1} 1749, 1655, 1618, 1546, 1454, 1374, 1233, 1171, 1052.

^1H NMR ($CDCl_3$) δ ppm 6.90 (H-11), 5.76 (H-10), 5.43 (H-13), 4.96 (8a-NH) exchangeable with D_2O, 4.89 (H-2'), 4.79 (H-4'), 4.66 (H-1"), 4.40 (H-1'), 4.18 (H-8), 3.55, 3.32 (H-2), 3.52 (3"-OCH_3), 3.49 (2"-OCH_3), 3.30

(20-OCH_3), 3.29 (20-OCH_3), 2.34 /3'-$N(CH_3)_2$/, 2.12 ($COCH_3$), 2.06 ($COCH_3$), 2.03 ($COCH_3$), 1.75 (H-22), 1.10 (H-21), 1.07 (H-18).

^{13}C NMR ($CDCl_3$) δ ppm 205.6 (C-3), 172.9 (C-1), 170.1, 169.8, 169.4 (3x$COCH_3$), 166.1 (9-CONH), 144.1 (C-11), 138.0 (C-13), 134.9 (C-12), 119.6 (C-10), 103.7 (C-20), 102.1 (C-1'), 100.9 (C-1"), 74.5 (C-4"), 71.4 (C-4'), 70.3 (C-2'), 61.3 (3"-OCH_3), 59.3 (2"-OCH_3), 53.7 (20-OCH_3), 50.6 (20-OCH_3), 46.5 (C-2), 44.2 (C-4), 42.0 (C-8), 41.0 /3'-$N(CH_3)_2$/, 34.5 (C-19), 21.9, (C-21), 21.1, 21.0, 20.7 (3x$COCH_3$), 17.6 (C-18), 12.7 (C-22).

FAB (MH^+) 957.

Example 8

4'-Demycarosyl-2',4',4"-tri-O-acetyl-3-deoxy-3-oxo-20-deoxo-20-dibenzylamino-8a-aza-8a-homotylosin (8)

A solution of pyridine trifluoroacetate (2.0 g, 10.36 mmol) in methylene chloride (10 ml) was added drop by drop at 15°C to a solution of the compound **4** (1.0 g, 1.09 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.04 g, 10.44 mmol) and dimethyl sulfoxide (1.6 ml, 22.56 mmol) in methylene chloride (20 ml). The reaction mixture was stirred for 6 hours at room temperature. The isolation of the product was carried out in the manner disclosed in Example 5. The obtained crude product (0.96 g) was purified by flash chromatography on a silica gel column using the solvent system B to give a TLC homogeneous product (**8**) (0.62 g).

TLC: Rf (B) 0.60.

IR (KBr) cm^{-1} 1748, 1633, 1538, 1454, 1373, 1231, 1052.

^1H NMR ($CDCl_3$) δ ppm 7.22 ~ 7.40 (phenyl), 6.89 (H-11), 5.66 (H-10), 5.49 (H-13), 4.96 (8a-NH) exchangeable with D_2O, 4.81 (H-2'), 4.74 (H-4'), 4.66 (H-1"), 4.42 (H-4"), 4.15 (H-1'), 4.12 (H-8), 3.78, 3.38 (H-2), 3.51 (2x20-N-CH_2-phenyl, 3"-OCH_3), 3.48 (2"-OCH_3), 2.32 /3'-$N(CH_3)_2$/, 2.22 (H-4), 2.09 ($COCH_3$), 2.06 ($COCH_3$), 2.00 ($COCH_3$), 1.72 (H-22), 1.10 (H-21), 1.08 (H-18).

^{13}C NMR ($CDCl_3$) δ ppm 206.7 (C-3), 172.7 (C-1), 170.1, 169.9, 169.5 (3x$COCH_3$), 166.1 (9-CONH), 144.0 (C-11),. 136.5 (C-12), 135.0 (C-13), 119.9 (C-10), 102.7 (C-1'), 100.9 (C-1"), 74.6 (C-4"), 71.3 (C-4'), 70.3 (C-2'), 61.3 (3"-OCH_3), 59.3 (2"-OCH_3), 51.7 (C-20), 47.7 (C-2), 44.5 (C-4)), 42.0 (C-8), 41.0 /3'-$N(CH_3)_2$/, 28.6 (C-19), 22.0 (C-21), 21.0, 20.7 (3x$COCH_3$), 17.8 (C-18), 13.1 (C-22),

20-$N(CH_2C_6H_2)$, 140.1, 128.9, 128.0, 126.4, 57.9.

FAB (MH^+) 1092.

Example 9

4'-Demycarosyl-4"-deoxy-4"-oxo-8a-aza-8a-homotylosin 20-dimethylacetal (9)

The compound 5 (0.65 g, 0.71 mmol) was dissolved in methanol (20 ml) and left to stand at room temperature for 48 hours. To the reaction solution a saturated $NaHCO_3$ solution was added and it was extracted twice with chloroform. The combined organic extracts were dried (K_2CO_3) and evaporated at reduced pressure to a dry residue. The obtained crude product (0.45 g) was purified by flash chromatography on a silica gel column using the solvent system A to give a TLC homogeneous product (9) (0.20 g).

TLC: Rf (A) 0.27.

IR (KBr) cm^{-1} 1749, 1657, 1620, 1542, 1455, 1375, 1230, 1172, 1060.

^{1}H NMR ($CDCl_3$) δ ppm 7.16 (H-11), 5.72 (H-10), 5.67 (H-13), 4.99 (8a-NH) exchangeable with D_2O, 4.60 (H-20), 4.63 (H-1"), 4.33 (H-1'), 4.17 (H-8), 3.98 (H-5"), 3.78 (H-3"), 3.58 (3"-OCH_3), 3.52 (2"-OCH_3), 3.46 (H-2'), 3.36, 3.35 (2x20-OCH_3), 3.30 (H-2"), 3.06 (H-4'), 2.33 /3'-$N(CH_3)_2$/, 1.76 (H-22), 1.34 (H-6"), 1.17 (H-21).

^{13}C NMR ($CDCl_3$) δ ppm 202.4 (C-4"), 173.1 (C-1), 166.1 (9-CONH), 144.6 (C-11), 137.6 (C-13), 135.3 (C-12), 119.5 (C-10), 103.6 (C-20), 103.0 (C-1"), 102.1 (C-1'), 85.3 (C-3"), 84.2 (C-2"), 73.3 (C-5"), 65.6 (C-3), 60.2 (3"-OCH_3), 59.1 (2"-OCH_3), 53.7 (20-OCH_3), 50.5 (20-OCH_3), 42.7 (C-8), 42.6 (C-4), 41.0

/3'-$N(CH_3)_2$/, 40.7 (C-2), 34.4 (C-19), 21.9 (C-21), 14.0 (C-6"), 12.7 (C-22), 8.3 (C-18).

FAB (MH^+) 831.

Example 10

4'-Demycarosyl-4"-deoxy-4"-oxo-20-deoxo-20-dibenzylamino-8a-aza-8a-homotylosin (10)

The compound 6 (0.30 g, 0.73 mmol) was dissolved in methanol (20 ml) and left to stand at room temperature for 30 hours. After addition of water (50 ml) the product was isolated by a gradient extraction with chloroform at pH 4.5 and 7.5. The combined chloroform extracts at pH 7.5 were dried (K_2CO_3) and evaporated at reduced pressure and the obtained product (0.17 g) was purified by flash chromatography on a silica gel column using the solvent system A to give a TLC homogeneous product (10) (0.08 g).

TLC: Rf (A) 0.49.

IR (KBr) cm^{-1} 1715, 1655, 1619, 1542, 1454, 1377, 1168, 1082.

^1H NMR ($CDCl_3$) δ ppm 7.25 ~ 7.41 (phenyl), 7.12 (H-11), 5.70 (H-13), 5.65 (H-10), 4.94 (8a-NH) exchangeable with D_2O, 4.84 (H-2'), 4.74 (H-4'), 4.60 (H-1"), 4.15 (H-1'), 3.98 (H-5"), 3.78 (H-3"), 3.62 (3"-OCH_3), 3.61 (20-N-CH_2-phenyl), 3.58 (20-CH_2-phenyl), 3.51 (2"-OCH_3), 3.46 (H-2'), 3.01 (H-4'), 2.32 /3'-$N(CH_3)_2$/, 1.72 (H-22), 1.12 (H-21).

^{13}C NMR ($CDCl_3$) δ ppm 202.4 (C-4"), 173.4 (C-1), 166.1 (9-CONH), 144.7 (C-11), 137.1 (C-13), 135.6 (C-12), 119.7 (C-10), 104.2 (C-1'), 103.0 (C-1"), 85.4 (C-3"), 84.9 (C-2"), 73.3 (C-5"), 66.4 (C-3), 59.8 (3"-OCH_3), 58.6 (2"-OCH_3), 52.2 (C-20), 43.3 (C-8), 42.3 (C-4), 41.5 /3'-$N(CH_3)_2$/, 38.7 (C-2), 29.4 (C-19), 22.0 (C-21), 14.1 (C-6"), 12.8 (C-22), 9.1 (C-18),
20-$N(CH_2C_6H_5)_2$ 139.8, 129.1, 128.0, 126.6, 58.0.

FAB (MH^+) 967.

Example 11

4'-Demycarosyl-4"-O-acetyl-3-deoxy-3-oxo-8a-aza-8a-homotylosin 20-dimethylacetal (11)

The compound 7 (0.70 g, 0.73 mmol) was dissolved in methanol (50 ml) and left to stand at room temperature for 24 hours. The isolation of the product was carried out in the manner disclosed in Example 9 and the obtained crude product (0.62 g) was purified by flash chromatography on a silica gel column using the solvent system A to give a TLC homogeneous product (11) (0.40 g).

TLC: Rf (A) 0.44.

IR (KBr) cm^{-1} 1749, 1657, 1620, 1544, 1455, 1375, 1229, 1170, 1063.

^1H NMR ($CDCl_3$) δ ppm 6.87 (H-11), 5.77 (H-10), 5.44 (H-13), 5.18 (8a-NH) exchangeable with D_2O, 4.88 (H-2'), 4.64 (H-1"), 4.44 (H-4"), 4.30 (H-1'), 4.17 (H-8), 3.93 (H-5"), 3.89 (H-3"), 3.53 (3"-OCH_3), 3.50, 3.26 (H-2), 3.48 (2"-OCH_3), 3.30 (20-OCH_3), 3.29 (20-OCH_3), 2.53 /3'-$N(CH_3)_2$/, 2.12 ($COCH_3$), 1.75 (H-22), 1.25 (H-18).

^{13}C NMR ($CDCl_3$) δ ppm 205.4 (C-3), 172.9 (C-1), 170.1 ($COCH_3$), 167.4 (9-CONH), 143.4 (C-11), 136.2 (C-12), 134.6 (C-13), 120.7 (C-10), 104.2 (C-1'), 103.9 (C-20), 100.8 (C-1"), 74.5 (C-4"), 70.9 (C-2'), 70.5 (C-2'), 61.3 (3"-OCH_3), 59.0 (2"-OCH_3), 52.6 (20-OCH_3), 52.1 (20-OCH_3), 45.9 (C-2), 44.4 (C-4), 42.5 (C-8), 41.4 /3'-$N(CH_3)_2$/, 33.8 (C-19), 22.0 (C-21), 20.7 ($COCH_3$), 17.5 (C-18), 12.9 (C-22).

FAB (MH^+) 873.

Example 12

4'-Demycarosyl-4"-O-acetyl-3-deoxy-3-oxo-20-deoxo-20-dibenzylamino-8a-aza-8a-homotylosin (12)

The compound **8** (1.20 g, 10.99 mmol) was dissolved in methanol (100 ml) and left to stand at room temperature for 24 hours. To the reaction solution water (100 ml) was added and it was extracted with methylene chloride at pH 6.5. The combined organic extracts were dried (K_2CO_3) and evaporated at reduced pressure and the obtained crude product (1.0 g) was purified by flash chromatography on a silica gel column using the solvent system A to give a TLC homogeneous product (**12**) (0.52 g).

TLC: Rf (A) 0.65.

IR (KBr) cm^{-1} 1745, 1650, 1622, 1537, 1454, 1373, 1233, 1166, 1058.

^1H NMR ($CDCl_3$) δ ppm 7.25 ~ 7.41 (phenyl), 6.90 (H-11), 5.67 (H-10), 5.52 (H-13), 4.98 (8a-NH) exchangeable with D_2O, 4.67 (H-1"), 4.45 (H-4"), 4.17 (H-1'), 4.02 (H-8), 3.61 (20-CH_2-phenyl), 3.53 (3"-OCH_3), 3.52 (20-CH_2-phenyl), 3.50 (2"-OCH_3), 3.76, 3.32 (H-2), 2.52 /3'-$N(CH_3)_2$/, 2.12 ($COCH_3$), 1.73 (H-22), 1.21 (H-18), 1.08 (H-21).

^{13}C NMR ($CDCl_3$) δ ppm 205.3 (C-3), 172.5 (C-1), 170.1 ($COCH_3$), 167.2 (9-CONH), 143.9 (C-11), 135.9 (C-12), 135.4 (C-13), 120.0 (C-10), 103.9 (C-1'), 100.9 (C-1"), 74.6 (C-4"), 70.7 (C-4'), 70.4 (C-2'), 61.3 (3"-OCH_3), 59.3 (2"-OCH_3), 51.6 (C-20), 46.1 (C-2), 44.5 (C-4), 43.3 (C-8), 41.5 /3'-$N(CH_3)_2$/, 28.8 (C-19), 22.0 (C-21), 20.7 ($COCH_3$), 17.8 (C-18), 12.9 (C-22), 20-$N(CH_2C_6H)_2$ 139.9, 128.8, 128.0, 126.5, 58.0.

FAB (MH^+) 1008.

Example 13

4'-Demycarosyl-4"-O-acetyl-8a-aza-8a-homotylosin 20-dimethylacetal (13)

The compound **3** (0.5 g, 0.52 mmol) was dissolved in methanol (20 ml) and left to stand at room temperature for 24 hours. The isolation of the product was carried out in the manner disclosed in Example 9 and the obtained crude product (0.43 g) was purified by flash chromatography on a silica gel column using the solvent system A to give a TLC homogeneous product (**13**) (0.32 g).

TLC: Rf (A) 0.32.

IR (KBr) cm^{-1} 1739, 1656, 1616, 1541, 1455, 1376, 1237, 1170, 1062.

^1H NMR ($CDCl_3$) δ ppm 7.15 (H-11), 5.71 (H-10), 5.66 (H-13), 4.97 (8a-NH) exchangeable with D_2O, 4.64 (H-1"), 4.62 (H-20), 4.44 (H-4"), 4.24 (H-1'), 4.18 (H-8), 3.53 (3"-OCH_3), 3.47 (2"-OCH_3), 3.37 (20-OCH_3), 3.36 (20-OCH_3), 2.50 /3'-$N(CH_3)_2$/, 2.12 ($COCH_3$), 1.75 (H-22), 1.17 (H-21).

FAB (MH^+) 875.

Example 14

4'-Demycarosyl-4"-O-acetyl-20-deoxo-20-dibenzylamino-8a-aza-8a-homotylosin (14)

The compound 4 (0.75 g, 0.69 mmol) was dissolved in methanol (20 ml) and left to stand at room temperature for 24 hours. The isolation of the product was carried out in the manner disclosed in Example 12 and the obtained crude product (0.66 g) was purified by flash chromatography on a silica gel column using the solvent system A to give a TLC homogeneous product (**14**) (0.45 g).

TLC: Rf (A) 0.50.

IR (KBr) cm^{-1} 1740, 1657, 1621, 1538, 1454, 1373, 1236, 1169, 1054.

^1H NMR ($CDCl_3$) δ ppm 7.25 ~ 7.41 (phenyl), 7.10 (H-11), 5.69 (H-13), 5.65 (H-10), 4.96 (8a-NH) exchangeable with D_2O, 4.66 (H-1"), 4.45 (H-4"), 4.14 (H-8), 4.07 (H-1'), 3.59 (20-N-CH_2-phenyl), 3.56 (20-CH_2-phenyl), 3.53 (3"-OCH_3), 3.50 (2"-OCH_3), 2.49 /3'-$N(CH_3)_2$/, 2.12 ($COCH_3$), 1.73 (H-22), 1.11 (H-21), 0.94 (H-18).

FAB (MH^+) 1010.

Example 15

4'-Demycarosyl-3-deoxy-3-oxo-8a-aza-8a-homotylosin 20-dimethylacetal (15)

The compound **11** (0.40 g, 0.46 mmol) was dissolved in a methanol/conc. NH_4OH mixture (4:1, 50 ml) and left to stand for 60 hours at the temperature of 5°C. The reaction solution was evaporated to an oily residue and then a product was isolated in the manner disclosed in Example 9. The obtained crude product (0.25 g) was purified by flash chromatography on a silica gel column using the solvent system A to give a TLC homogeneous product (**15**) (0.15 g).

TLC: Rf (A) 0.39.

IR (KBr) cm^{-1} 1739, 1714, 1650, 1620, 1544, 1455, 1375, 1170, 1063.

^1H NMR ($CDCl_3$) δ ppm 6.87 (H-11), 5.77 (H-10), 5.44 (H-13), 5.18 (8a-NH) exchangeable with D_2O, 4.60 (H-20), 4.64 (H-1"), 4.33 (H-1'), 4.17 (H-8), 3.93 (H-5"), 3.89 (H-3"), 3.53 (3"-OCH_3), 3.50, 3.26 (H-2), 3.48 (2"-OCH_3), 3.30 (20-OCH_3), 3.29 (20-OCH_3), 2.33 /3'-$N(CH_3)_2$/, 1.75 (H-22), 1.25 (H-18).

FAB (MH^+) 831.

Example 16

4'-Demycarosyl-3-deoxy-3-oxo-20-deoxo-20-dibenzylamino-8a-aza-8a-homotylosin (16)

The compound **12** (0.78 g, 0.77 mmol) was dissolved in a methanol/conc. NH_4OH mixture (4:1, 50 ml) and left to stand for 24 hours at room temperature. To the reaction solution water (80 ml) was added and it was extracted twice with methylene chloride at pH 7.5. The combined organic extracts were dried (K_2CO_3) and evaporated at reduced pressure and the obtained product (0.66 g) was purified by flash chromatography on a silica gel column using the solvent system A to give a TLC homogeneous product (**16**) (0.32 g).

TLC: Rf (A) 0.55.

IR (KBr) cm^{-1} 1739, 1714, 1650, 1622, 1538, 1454, 1376, 1167, 1082.

^1H NMR ($CDCl_3$) δ ppm 7.25 ~ 7.41 (phenyl), 6.90 (H-11), 5.66 (H-13), 5.53 (H-10), 5.28 (8a-NH) exchangeable with D_2O, 4.61 (H-1"), 4.16 (H-1'), 4.03 (H-8),

3.62 (20-N-CH_2-phenyl), 3.61 (20-CH_2-phenyl, 3"-OCH_3), 3.51 (2"-OCH_3), 3.78, 3.38 (H-2), 2.5 /3'-$N(CH_3)_2$/, 2.38 (H-4), 1.72 (H-22), 1.21 (H-18), 1.08 (H-21).

^{13}C NMR ($CDCl_3$) δ ppm 205.3 (C-3), 172.5 (C-1), 167.2 (9-CONH), 143.9 (C-11), 135.9 (C-12), 135.6 (C-13), 120.0 (C-10), 103.9 (C-1'), 101.0 (C-1'), 72.5 (C-4"), 70.7 (C-4'), 70.4 (C-2'), 61.5 (3"-OCH_3), 59.5 (2"-OCH_3), 51.7 (C-20), 46.1 (C-2), 44.5 (C-4), 43.3 (C-8), 41.5 /3'-$N(CH_3)_2$/, 28.8 (C-19), 22.0 (C-21), 17.8 (C-18), 12.9 (C-22),

20-$N(CH_2C_6H)_2$ 140.0, 128.8, 128.0, 126.5, 58.0.

FAB (MH^+) 967.

Example 17

4'-Demycarosyl-3-deoxy-3-oxo-8a-aza-8a-homotylosin (17)

The compound **15** (0.5 g, 0.60 mmol) was dissolved in an acetonitrile/0.1 N HCl mixture (1:1, 35 ml) and stirred for 2 hours at room temperature. To the reaction solution a saturated $NaHCO_3$ solution was added and it was extracted twice with methylene chloride. The combined organic extracts were dried (K_2CO_3) and evaporated at reduced pressure and the obtained product (0.42 g) was purified by flash chromatography on a silica gel column using the solvent system A to give a TLC homogeneous product (**17**) (0.25 g).

TLC: Rf (A) 0.35.

IR (KBr) cm^{-1} 1739, 1719, 1657, 1620, 1545, 1455, 1376, 1169, 1082.

^1H NMR ($CDCl_3$) δ ppm 9.78 (H-20), 7.19 (H-11), 5.72 (H-10), 5.70 (H-13), 5.06 (8a-NH) exchangeable with D_2O, 4.58 (H-1"), 4.18 (H-1'), 4.23 (H-8), 3.68, 3.32 (H-2), 3.62 (3"-OCH_3), 3.49 (2"-OCH_3), 2.49 /3'-$N(CH_3)_2$/, 1.75 (H-22), 1.25 (H-18), 1.18 (H-21).

^{13}C NMR ($CDCl_3$) δ ppm 205.3 (C-3), 203.8 (C-20), 173.5 (C-1), 166.9 (9-CONH), 145.1 (C-11), 138.2 (C-13), 135.1 (C-12), 129.3 (C-10), 103.7 (C-1'), 101.1 (C-1'), 72.8 (C-4"), 71.0 (C-4'), 70.4 (C-2'), 61.5 (3"-OCH_3), 59.5 (2"-OCH_3),

46.6 (C-19), 46.1 (C-2), 44.5 (C-4), 43.3 (C-8), 41.5 /3'-$N(CH_3)_2$/, 22.4 (C-21), 17.8 (C-18), 12.9 (C-22).

FAB (MH^+) 785.

Example 18

4'-Demycarosyl-2',4'-di-O-acetyl-8a-aza-8a-homotylosin (18)

The compound **1** (0.5 g, 0.55 mmol) was dissolved in an acetonitrile/0.1 N HCl mixture (1:1, 35 ml) and stirred for 2 hours at room temperature. The isolation of the product was carried out in the manner disclosed in Example 17 to give a TLC homogeneous product (**18**) (0.34 g).

TLC: Rf (B) 0.35.

IR (KBr) cm^{-1} 1749, 1657, 1620, 1548, 1455, 1375, 1231, 1170, 1059.

^1H NMR ($CDCl_3$) δ ppm 9.75 (H-20), 7.21 (H-11), 5.72 (H-10), 5.71 (H-13), 5.08 (8a-NH) exchangeable with D_2O, 4.89 (H-2'), 4.74 (H-4'), 4.58 (H-1"), 4.26 (H-1'), 3.61 (3"-OCH_3), 3.49 (2"-OCH_3), 2.33 /3'-$N(CH_3)_2$/, 2.05 ($COCH_3$), 2.03 ($COCH_3$), 1.74 (H-22), 1.18 (H-21).

^{13}C NMR ($CDCl_3$) δ ppm 203.6 (C-20), 173.3 (C-1), 169.9, 169.5 (2x$COCH_3$), 166.5 (9-CONH), 145.2 (C-11), 138.3 (C-13), 135.0 (C-12), 119.0 (C-10), 101.6 (C-1'), 100.9 (C-1"), 72.5 (C-4"), 70.6 (C-4'), 70.3 (C-2'), 65.6 (C-3), 61.5 (3"-OCH_3), 59.5 (2"-OCH_3), 46.3 (C-19), 42.5 (C-8), 41.0 /3'-$N(CH_3)_2$/, 38.5 (C-2), 21.6 (C-21), 21.1, 21.0 (2x$COCH_3$), 12.7 (C-22), 8.1 (C-18).

FAB (MH^+) 871.

Example 19

4'-Demycarosyl-2',4',4"-tri-O-acetyl-8a-aza-8a-homotylosin (19)

The compound **3** (0.5 g, 0.52 mmol) was dissolved in an acetonitrile/0.1 N HCl mixture (1:1, 35 ml) and stirred for 2 hours at room temperature. The isolation of the

product was carried out in the manner disclosed in Example 17 to give a TLC homogeneous product (**19**) (0.47 g).

TLC: Rf (B) 0.60; Rf (C) 0.50.

IR (KBr) cm^{-1} 1748, 1659, 1621, 1538, 1455, 1373, 1232, 1171, 1052.

^1H NMR ($CDCl_3$) δ ppm 9.74 (H-20), 7.16 (H-11), 5.69 (H-10), 5.65 (H-13), 4.89 (8a-NH) exchangeable with D_2O, 4.88 (H-2'), 4.76 (H-4'), 4.64 (H-1"), 4.44 (H-4"), 4.33 (H-1'), 4.18 (H-8), 3.52 (3"-OCH_3), 3.46 (2"-OCH_3), 2.33 /3'-$N(CH_3)_2$/, 2.12 ($COCH_3$), 2.05 ($COCH_3$), 2.03 ($COCH_3$), 1.74 (H-22), 1.16 (H-21).

^{13}C NMR ($CDCl_3$) δ ppm 203.6 (C-20), 173.1 (C-1), 170.1, 169.8, 169.4 (3x$COCH_3$), 166.1 (9-CONH), 144.7 (C-11), 138.0 (C-13), 134.9 (C-12), 119.2 (C-10), 103.7 (C-20), 102.1 (C-1'), 100.9 (C-1"), 74.5 (C-4"), 71.4 (C-4'), 70.3 (C-2'), 65.6 (C-3), 61.3 (3"-OCH_3), 59.3 (2"-OCH_3), 46.3 (C-19), 42.7 (C-8), 42.6 (C-4), 41.0 /3'-$N(CH_3)_2$/, 40.5 (C-2), 34.5 (C-19), 21.9 (C-21), 21.1, 21.0, 20.7 (3x$COCH_3$), 12.7 (C-22), 8.3 (C-18).

FAB (MH^+) 913.

Example 20

4'-Demycarosyl-2',4'-di-O-acetyl-4"-deoxy-4"-oxo-8a-aza-8a-homotylosin (20)

The compound **5** (0.7 g, 0.77 mmol) was dissolved in an acetonitrile/0.1 N HCl mixture (1:1, 50 ml) and stirred for 1 hour at room temperature. The isolation of the product was carried out in the manner disclosed in Example 17 to give a TLC homogeneous product (**20**) (0.36 g).

TLC: Rf (B) 0.48.

IR (KBr) cm^{-1} 1749, 1656, 1619, 1543, 1458, 1375, 1230, 1172, 1058.

^1H NMR ($CDCl_3$) δ ppm 9.75 (H-20), 7.21 (H-11), 5.72 (H-10), 5.70 (H-13), 5.08 (8a-NH) exchangeable with D_2O, 4.88 (H-2'), 4.74 (H-4'), 4.58 (H-1"), 4.30 (H-1'), 4.17 (H-8), 3.98 (H-5"), 3.78 (H-3"), 3.58 (3"-OCH_3), 3.48 (2"-OCH_3),

3.30 (H-2"), 2.33 /3'-N(CH_3)$_2$/, 2.05 ($COCH_3$), 2.03 ($COCH_3$), 1.76 (H-22), 1.34 (H-6"), 1.17 (H-21).

^{13}C NMR ($CDCl_3$) δ ppm 203.0 (C-20), 202.4 (C-4"), 173.1 (C-1), 169.9, 169.5 (2x$COCH_3$), 166.5 (9-CONH), 145.0 (C-11), 138.1 (C-13), 135.1 (C-12), 119.0 (C-10), 102.1 (C-1"), 100.9 (C-1'), 85.3 (C-3"), 84.2 (C-2"), 73.3 (C-5"), 71.3 (C-4'), 70.3 (C-2'), 65.6 (C-3), 61.5 (3"-OCH_3), 59.4 (2"-OCH_3), 46.3 (C-19), 42.5 (C-8), 41.0 /3'-N(CH_3)$_2$/, 38.5 (C-2), 21.9 (C-21), 21.1, 21.0 (2x$COCH_3$), 14.0 (C-6"), 12.7 (C-22), 8.3 (C-1).

FAB (MH^+) 869.

Example 21

4'-Demycarosyl-4"-O-acetyl-8a-aza-8a-homotylosin (21)

The compound **19** (0.30 g, 0.33 mmol) was dissolved in methanol (20 ml) and left to stand for 24 hours at room temperature. The isolation of the product was carried out in the manner disclosed in Example 9 and the obtained crude product (0.25 g) was purified by flash chromatography on a silica gel column using the solvent system A to give a TLC homogeneous product (**21**) (0.19 g).

TLC: Rf (A) 0.28.

IR (KBr) cm^{-1} 1749, 1657, 1620, 1544, 1455, 1375, 1229, 1170, 1063.

^{1}H NMR ($CDCl_3$) δ ppm 9.78 (H-20), 7.20 (H-11), 5.72 (H-10), 5.70 (H-13), 5.12 (8a-NH) exchangeable with D_2O, 4.88 (H-2'), 4.64 (H-1"), 4.44 (H-4"), 4.18 (H-1'), 4.12 (H-8), 3.93 (H-5"), 3.89 (H-3"), 3.53 (3"-OCH_3), 3.48 (2"-OCH_3), 2.49 /3'-N(CH_3)$_2$/, 2.12 ($COCH_3$), 1.75 (H-22).

FAB (MH^+) 829.

Example 22

4'-Demycarosyl-4"-deoxy-4"-oxo-8a-aza-8a-homotylosin (22)

The compound **20** (0.23 g, 0.27 mmol) was dissolved in methanol (20 ml) and left to stand for 24 hours at room temperature. The isolation of the product was carried out in the manner disclosed in Example 9 and the obtained crude product (0.14 g) was purified by flash chromatography on a silica gel column using the solvent system A to give a TLC homogeneous product (**22**) (0.095 g).

TLC: Rf (A) 0.30.

IR (KBr) cm^{-1} 1717, 1655, 1625, 1542, 1454, 1378, 1170, 1062.

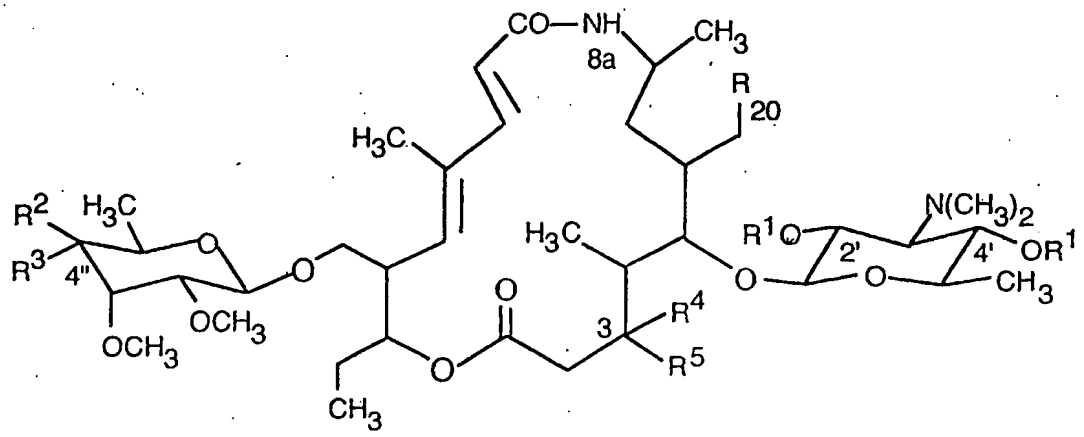
^1H NMR ($CDCl_3$) δ ppm 9.76 (H-20), 7.20 (H-11), 5.72 (H-10), 5.70 (H-13), 5.12 (8a-NH) exchangeable with D_2O, 4.64 (H-1"), 4.33 (H-1'), 4.18 (H-8), 3.98 (H-5"), 3.78 (H-3"), 3.58 (3"-OCH_3), 3.46 (2"-OCH_3), 3.30 (H-2"), 3.06 (H-4'), 2.33 /3'-$N(CH_3)_2$/, 1.74 (H-22), 1.34 (H-6"), 1.16 (H-21).

^{13}C NMR ($CDCl_3$) δ ppm 203.7 (C-20), 202.5 (C-4"), 173.4 (C-1), 166.6 (9-CONH), 144.9 (C-11), 137.6 (C-13), 135.4 (C-12), 119.4 (C-10), 102.1 (C-1'), 100.9 (C-1"), 71.4 (C-4'), 70.3 (C-2'), 66.3 (C-3), 61.5 (3"-OCH_3), 59.7 (2"-OCH_3), 46.2 (C-19), 42.7 (C-8), 42.1 (C-4), 41.5 /3'-$N(CH_3)_2$/, 39.8 (C-2), 21.7 (C-21), 14.0 (C-6"), 12.7 (C-22), 8.7 (C-18).

FAB (MH^+) 785.

CLAIMS

1. Compounds of the general formula I



I

wherein R represents CHO, $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$,
R^1 represents H or C_1-C_3 acyl,
R^2 represents OR^6 and R^6 represents H or C_1-C_3 acyl,
R^3 represents H or R^2 and R^3 together represent =O,
R^4 represents OH,
R^5 represents H or R^4 and R^5 together represent =O.

2. A compound according to claim 1, characterized in that R represents $CH(OCH_3)_2$, R^1 represents $COCH_3$, R^2 represents OR^6 wherein R^6 represents H, R^3 and R^5 are the same and represent H and R^4 represents OH.

3. A compound according to claim 1, characterized in that R represents $CH_2N[CH_2(C_6H_5)]_2$, R^1 represents $COCH_3$, R^2 represents OR^6 wherein R^6 represents H, R^3 and R^5 are the same and represent H and R^4 represents OH.

4. A compound according to claim 1, characterized in that R represents $CH(OCH_3)_2$, R^1 represents $COCH_3$, R^2 represents OR^6 wherein R^6 represents $COCH_3$, R^3 and R^5 are the same and represent H and R^4 represents OH.

5. A compound according to claim 1, characterized in that R represents $CH_2N[CH_2(C_6H_5)]_2$, R^1 represents $COCH_3$, R^2 represents OR^6 wherein R^6 represents $COCH_3$, R^3 and R^5 are the same and represent H and R^4 represents OH.

6. A compound according to claim 1, characterized in that R represents $CH(OCH_3)_2$, R^1 represents $COCH_3$, R^2 and R^3 together represent =O, R^4 represents OH and R^5 represents H.

7. A compound according to claim 1, characterized in that R represents $CH_2N[CH_2(C_6H_5)]_2$, R^1 represents $COCH_3$, R^2 and R^3 together represent =O, R^4 represents OH and R^5 represents H.

8. A compound according to claim 1, characterized in that R represents $CH(OCH_3)_2$, R^1 represents $COCH_3$, R^2 represents OR^6 wherein R^6 represents $COCH_3$, R^3 represents H and R^4 and R^5 together represent =O.

9. A compound according to claim 1, characterized in that R represents $CH_2N[CH_2(C_6H_5)]_2$, R^1 represents $COCH_3$, R^2 represents OR^6 wherein R^6 represents $COCH_3$, R^3 represents H and R^4 and R^5 together represent =O.

10. A compound according to claim 1, characterized in that R represents $CH(OCH_3)_2$, R^1 and R^5 are the same and represent H, R^2 and R^3 together represent =O and R^4 represents OH.

11. A compound according to claim 1, characterized in that R represents $CH_2N[CH_2(C_6H_5)]_2$, R^1 and R^5 are the same and represent H, R^2 and R^3 together represent =O and R^4 represents OH.

12. A compound according to claim 1, characterized in that R represents $CH(OCH_3)_2$, R^1 and R^3 are the same and represent H, R^2 represents OR^6 wherein R^6 represents $COCH_3$, and R^4 and R^5 together represent =O.

13. A compound according to claim 1, characterized in that R represents $CH_2N[CH_2(C_6H_5)]_2$, R^1 and R^3 are the same and represent H, R^2 represents OR^6 wherein R^6 represents $COCH_3$, and R^4 and R^5 together represent =O.

14. A compound according to claim 1, characterized in that R represents $CH(OCH_3)_2$, R^1, R^3 and R^5 are the same and represent H, R^2 represents OR^6 wherein R^6 represents $COCH_3$, and R^4 represents OH.

15. A compound according to claim 1, characterized in that R represents $CH_2N[CH_2(C_6H_5)]_2$, R^1, R^3 and R^5 are the same and represent H, R^2 represents OR^6 wherein R^6 represents $COCH_3$, and R^4 represents OH.

16. A compound according to claim 1, characterized in that R represents $CH(OCH_3)_2$, R^1 and R^3 are the same and represent H, R^2 represents OR^6 wherein R^6 represents H, and R^4 and R^5 together represent =O.

17. A compound according to claim 1, characterized in that R represents $CH_2N[CH_2(C_6H_5)]_2$, R^1 and R^3 are the same and represent H, R^2 represents OR^6 wherein R^6 represents H, and R^4 and R^5 together represent =O.

18. A compound according to claim 1, characterized in that R represents CHO, R^1 and R^3 are the same and represent H, R^2 represents OR^6 wherein R^6 represents H, and R^4 and R^5 together represent =O.

19. A compound according to claim 1, characterized in that R represents CHO, R^1 represents $COCH_3$, R^2 represents OR^6 wherein R^6 represents H, R^3 and R^5 are the same and represent H and R^4 represents OH.

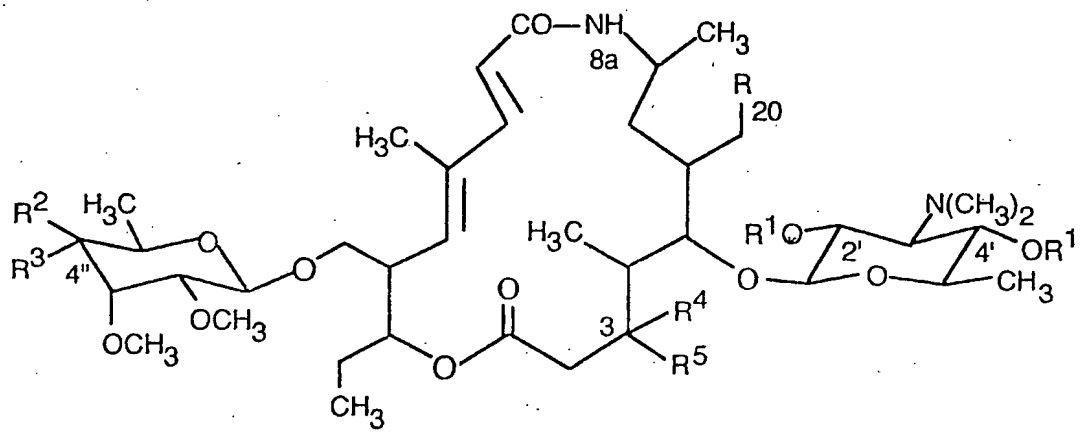
20. A compound according to claim 1, characterized in that R represents CHO, R^1 represents $COCH_3$, R^2 represents OR^6 wherein R^6 represents $COCH_3$, R^3 and R^5 are the same and represent H and R^4 represents OH.

21. A compound according to claim 1, characterized in that R represents CHO, R^1 represents $COCH_3$, R^2 and R^3 together represent =O, R^4 represents OH and R^5 represents H.

22. A compound according to claim 1, characterized in that R represents CHO, R^1, R^3 and R^5 are the same and represent H, R^2 represents OR^6 wherein R^6 represents $COCH_3$, and R^4 represents OH.

23. A compound according to claim 1, characterized in that R represents CHO, R^1 and R^5 are the same and represent H, R^2 and R^3 together represent =O and R^4 represents OH.

24. Process for the preparation of the compounds of the general formula I



I

wherein R represents CHO, $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$,

R^1 represents H or C_1-C_3 acyl,

R^2 represents OR^6 and R^6 represents H or C_1-C_3 acyl,

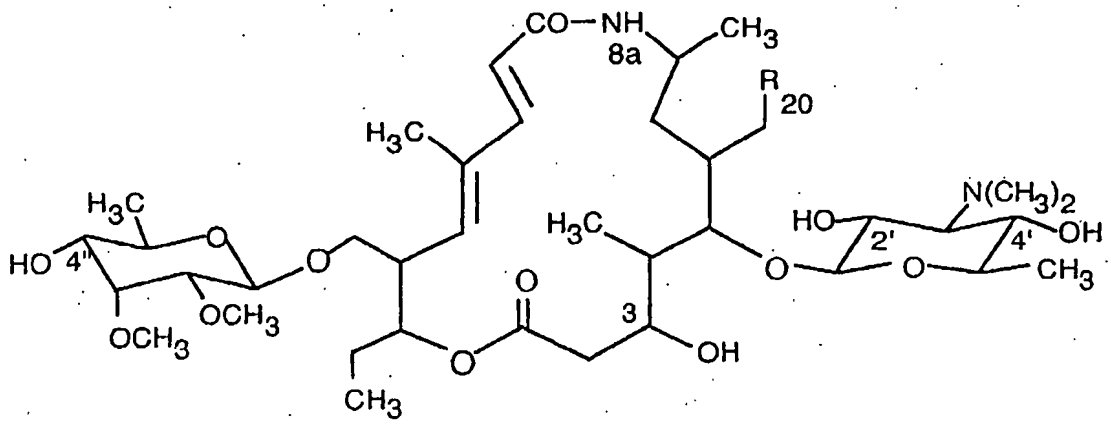
R^3 represents H or R^2 and R^3 together represent =O,

R^4 represents OH,

R^5 represents H or R^4 and R^5 together represent =O,

characterized in that

4'-demycarosyl-8a-aza-8a-homotylosin 20-dimethylacetal of the formula IIa and 4'-demycarosyl-20-deoxo-20-dibenzylamino-8a-aza-8a-homotylosin of the formula IIb



IIa R = $CH(OCH_3)_2$

IIb R = $CH_2N[CH_2(C_6H_5)]_2$

are subjected to

A) an O-acylation with anhydrides of C_1-C_3 carboxylic acids, preferably with acetic acid anhydride in methylene chloride during 15 minutes to 1 hour at room temperature, and the obtained compounds of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1 represents $COCH_3$, R^2 represents OR^6, wherein R^6 represents H, R^3 and R^5 are the same and represent H and R^4 represents OH,

are optionally subjected to

A1) an O-acylation with anhydrides of C_1-C_3 carboxylic acids, preferably with acetic acid anhydride in methylene chloride in the presence of an organic base, preferably triethyl amine and 4-dimethylaminopyridine as a catalyst during 30 hours at room temperature, and the obtained compounds of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1 represents $COCH_3$, R^2 represents OR^6, wherein R^6 represents $COCH_3$, R^3 and R^5 are the same and represent H and R^4 represents OH,

are optionally subjected to

B) an oxidation reaction with N(3-dimethylamino-propyl)-N'ethyl carbodiimide hydrochloride in the presence of dimethylsulfoxide and pyridine trifluoroacetate as a catalyst in an inert solvent, preferably methylene chloride, during 2 to 6 hours at a temperature from 10°C to room temperature, and the obtained compounds of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1 represents $COCH_3$, R^2 represents OR^6, wherein R^6 represents $COCH_3$, R^3 represents H and R^4 and R^5 together represent =O,

are optionally subjected to

C) methanolysis at room temperature for 2 days and the obtained compounds of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1 and R^3 are the same and represent H, R^2 represents OR^6, wherein R^6 represents $COCH_3$, and R^4 and R^5 together represent =O,

are optionally subjected to

C1) an alkaline methanolysis in a mixture of methanol and 25% ammonia (4:1) at a temperature from 5°C to room temperature during 20 to 60 hours to obtain compounds of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1 and R^3 are the same and represent H, R^2 represents OR^6, wherein R^6 represents H, and R^4 and R^5 together represent =O;

or the compound obtained according to process C1

of the formula I, wherein R represents $CH(OCH_3)_2$, R^1 and R^3 are the same and represent H, R^2 represents OR^6, wherein R^6 represents H, and R^4 and R^5 together represent =O,

is optionally subjected to

D) a hydrolysis of the acetal in a mixture of acetonitrile and 0.1 N hydrochloric acid (1:1) for 2 hours at room temperature to obtain the compound of the formula I, wherein R represents a CHO group, R^1 and R^3 are the same and represent H, R^2 represents OR^6, wherein R^6 represents H, and R^4 and R^5 together represent =O;

or compounds obtained according to process A
of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1 represents $COCH_3$, R^2 represents OR^6, wherein R^6 represents H, R^3 and R^5 are the same and represent H and R^4 represents OH,

are optionally subjected to oxidation in the manner disclosed in B,
and the obtained compounds of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1 represents $COCH_3$, R^2 and R^3 together represent =O, R^4 represents OH and R^5 represents H,

are optionally subjected to methanolysis in the manner disclosed in C,
to obtain compounds of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1 and R^5 are the same and represent H, R^2 and R^3 together represent =O and R^4 represents OH;

or the compound obtained according to process B
of the formula I, wherein R represents a $CH(OCH_3)_2$ group, R^1 represents $COCH_3$, R^2 and R^3 together represent =O, R^4 represents OH and R^5 represents H,

is optionally subjected to a hydrolysis of acetal in the manner disclosed in D,
and the obtained compound of the formula I, wherein R represents a CHO group, R^1 represents $COCH_3$, R^2 and R^3 together represent =O, R^4 represents OH and R^5 represents H,

is optionally subjected to methanolysis in the manner disclosed in C,
to obtain the compound of the formula I, wherein R represents a CHO group, R^1 and R^5 are the same and represent H, R^2 and R^3 together represent =O and R^4 represents OH;

or the compound obtained according to process A

of the formula I, wherein R represents $CH(OCH_3)_2$, R^1 represents $COCH_3$, R^2 represents OR^6, wherein R^6 represents H, R^3 and R^5 are the same and represent H and R^4 represents OH,

is optionally subjected to a hydrolysis of acetal in the manner disclosed in D,
to obtain a compound of the formula I wherein R represents CHO, R^1 represents $COCH_3$, R^2 represents OR^6, wherein R^6 represents H, R^3 and R^5 are the same and represent H and R^4 represents OH;

or compounds obtained according to process A1
of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1 represents $COCH_3$, R^2 represents OR^6, wherein R^6 represents $COCH_3$, R^3 and R^5 are the same and represent H and R^4 represents OH,

are optionally subjected to methanolysis in the manner disclosed in C,
to obtain compounds of the formula I, wherein R represents $CH(OCH_3)_2$ or $CH_2N[CH_2(C_6H_5)]_2$, R^1, R^3 and R^5 are the same and represent H, R^2 represents OR^6, wherein R^6 represents $COCH_3$, and R^4 represents OH;

or the compound obtained according to process A1
of the formula I, wherein R represents $CH(OCH_3)_2$, R^1 represents $COCH_3$, R^2 represents OR^6, wherein R^6 represents $COCH_3$, R^3 and R^5 are the same and represent H and R^4 represents OH,

is optionally subjected to a hydrolysis of acetal in the manner disclosed in D,
and the obtained compound of the formula I, wherein R represents CHO, R^1 represents $COCH_3$, R^2 represents OR^6, wherein R^6 represents $COCH_3$, R^3 and R^5 are the same and represent H and R^4 represents OH,

is optionally subjected to methanolysis in the manner disclosed in C,

to obtain the compound of the formula I, wherein R represents CHO, R^1, R^3 and R^5 are the same and represent H, R^2 represents OR^6, wherein R^6 represents $COCH_3$, and R^4 represents OH.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/HR 00/00018

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H17/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GRDISA, MIRA ET AL: "Effect of a 17-member azalide on tumor cell growth" CHEMOTHERAPY (BASEL) (1998), 44(5), 331-336 , 1998, XP000940917 the whole document ---	1
X	EP 0 410 433 A (PLIVA PHARM & CHEM WORKS) 30 January 1991 (1991-01-30) cited in the application compounds Ic, Id claim 1 ---	1
A	EP 0 287 082 A (PLIVA PHARM & CHEM WORKS) 19 October 1988 (1988-10-19) cited in the application --- -/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bardili, W

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